110. (Amended) A method of treating [Crohn's] TNFα-mediated disease in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody competitively inhibits binding of TNF to a monoclonal antibody selected from the group consisting of A2 or cA2.

111. (Amended) A method of treating [Crohn's] TNFα-mediated disease in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody, wherein said anti-TNF chimeric antibody binds to one or more epitopes included in amino acids between 87-108 or both 59-80 and 87-108 of SEQ ID NO.:1 of hTNF.

112. (Amended) A method of treating [Crohn's] TNFα-mediated disease in a human comprising administering to the human an effective TNF-inhibiting amount of chimeric anti-TNF antibody cA2.

REMARKS

Claim Amendments

Claims 106, 109, 110, 111 and 112 have been amended. Claims 106, 110, 111, and 112 have been amended to recite a method of treating TNFα-mediated disease. Claim 109 has been amended to correct a typographical error. Claim 96 has been further amended to recite that the anti-TNF chimeric antibody binds to one or more epitopes included in the recited subsequences of amino acids. Support for these claims is found throughout the Specification. No new matter has been added. Since the amended claims generically embrace the examined claims no shift in invention has been raised by the amendment. Entry and examination under 37 C.F.R. § 1.112 is requested.

Informalities

Amendments to the specification have been made to correct informalities and to help conform the numbering in the specification of the figures to the actual numbers of the figures.

Title

The title of the invention has been amended to be more clearly indicative of the invention to which the elected claims are directed, as requested by the Examiner.

Objection to Drawings

Applicants acknowledge the objection to the drawings. As is customary, formal drawings will be filed at the time of notice of allowable subject matter.

Notice of Informal Patent Application

The Office Action states that a Notice of Informal Patent Application was attached thereto. However, such a Notice was not received. A copy is requested.

Sequence Listing

The Examiner has directed Applicants' attention to a Preliminary Amendment filed April 14, 1994, which amended the page numbering of the specification to coincide with that of a new sequence listing which was submitted with the April 14, 1994 amendment. He remarked that the computer print out dated April 21, 1995, which appears to correspond to the sequence listing listed in the April 14, 1994 Preliminary Amendment, has 7 pages, although the amendment requires the specification to be renumbered 150-156. Since the sequence listing did not appear to correspond with the amendment, he requested clarification and/or submission of a copy of the amendment in the original form.

Applicants' copy of the file history does not include a computer print-out dated April 21, 1995. As such, Applicants are

unable to address the concern raised by the Examiner. Applicants intend to submit an amended sequence listing to correct the number of sequences as well as the correspondence address, and to supply current application data in the near future.

Information Disclosure Statement

The Examiner has correctly acknowledged the IDS's for this application, filed August 4, 1995, and January 30, 1995. The Examiner states that "several references have been listed on the PTO-892, but have not actually been provided." Applicants do not understand. Neither the IDS dated August 4, 1995, nor the IDS dated January 30, 1995 contain the references listed on the PTO-892 provided by the Examiner. Although the Examiner stated that these citations have been crossed out on Applicants' copy of the initialed 1449, no initialed 1449 was included in the Examiner's Office Action. Applicants hereby request that the Examiner return initialed copies of the 1449 forms for the IDS's filed August 4, 1995 and January 30, 1995, to provide a record that the Examiner considered the references cited.

Provisional Double Patenting

Claims 106-112 have been provisionally rejected under 35 U.S.C. §101 as claiming the same invention as that of Claims 91-97 in co-pending application Serial No. 08/192,102, because the claims in each application are identical to each other. Claims 106-112 have been amended so that they are no longer identical to Claims 91-97 in the co-pending application. Further, upon resolution of the remaining rejections of record and in the event that the claims remain pending in the '102 application, a terminal disclaimer will be submitted.

Priority

The Examiner stated that applications Serial Nos. 07/670,827 (filed March 18, 1991) and 07/853,606 (filed March 18, 1992) fail to provide a disclosure of the claimed antibody in Crohn's

disease and fail to disclose Crohn's disease as a preferred embodiment, and that, consequently, the priority of the claimed invention does not enjoy the benefit of these applications.

Applicants respectfully disagree and have addressed this assertion in Serial No. 08/192,102.

Since Claims 106, 109, 110, 111 and 112 have been amended to claim methods of treating TNFα-mediated disease, and the specifications in the above-cited applications, refer to treatment of a subject having a pathology, disease or condition associated with excessive levels of TNF, the assertion is moot. Applicants request acknowledgement by the PTO that the present claims are entitled to the earliest claimed priority date.

Objection to the Specification and Rejection of Claims 108 and 110 Under 35 U.S.C. §112, First Paragraph, Deposit

The specification and Claims 108 and 110 have been objected to as lacking enablement of the cA2 antibody absent a deposit of the antibody and the hybridoma cell line producing the antibody. The Examiner stated that the Rademacher reference teaches that the specific glycosylation of the antibody is important to the instant case. The Examiner then asserted that antibodies produced recombinantly will often have aberrant glycosylation or no glycosylation depending on the host in which said antibody is produced.

The Rademacher reference does not indicate that the glycosylation of the administered antibody is important, but merely indicates the presence of the agalactosyl IgG in an animal with Crohn's disease. The author merely speculated that this fact *may* contribute to disease pathogenesis. (Page 246, last paragraph). However, association of an endogenous agalactosyl antibody with Crohn's disease does not establish the role of the agalactosyl antibody in the disease. Furthermore, the glycosylation of antibodies produced by an animal who has Crohn's disease is not relevant to the determination of requisite characteristics of antibodies administered to treat that disease

or any other TNFα-mediated disease. That is, the agalactosyl antibody referred to by the reference was not administered to treat the disease but was present in the animal with the disease. Thus, the reference is immaterial to the issue posed by the Examiner.

Furthermore, even if glycosylation of the administered antibodies is important to the claimed invention, Applicants have sufficiently disclosed the methods of production of chimeric anti-TNF antibodies to achieve proper glycosylation. For example, on page 52, line 12, of Applicants' specification, the Applicants disclose that the preferred recipient cell line for transfection of the expression vectors and production of the chimeric antibody is the myeloma cell. The specification indicates that myeloma cells can synthesize, assemble and secrete immunoglobulins encoded by transfected immunoglobulin genes and possess the mechanism for glycosylation of the immunoglobulin. (Page 52, lines 12-15). It particularly indicates that the preferred recipient cell is the recombinant Ig-producing myeloma cell SP2/0 (ATCC # CRL 8287). It also indicates that the immunoglobulin genes of the present invention can also be expressed in yeast cells, and that these cells carried out post-translational peptide modifications including glycosylation. (Page 53, lines 20-22). Finally, on page 54, lines 27-31, it indicates that "mammalian cells provide post-translational modifications to immunoglobulin protein molecules including leader peptide removal, folding and assembly of HL chains, glycosylation of the antibody molecules, and secretion of functional antibody protein."

"No deposit is necessary if the biological organisms can be obtained from readily available sources or derived from readily available starting materials through routine screening that does not require undue experimentation." In re Wands, 8 U.S.P.Q.2d 1400, 1403 (Fed. Cir. 1988). Since the specification provides significant description of the properties (e.g., glycosylation, epitopic specificity and affinity) of the chimeric anti-TNF

antibodies, the screening of antibodies which have the same or similar properties does not require undue experimentation. As such, no deposit is required. Accordingly, to the best of knowledge of the undersigned, neither the c134A nor the c168A cell line has been deposited in the ATCC collection.

Withdrawal of the rejection of Claims 108 and 110 and withdrawal of the objection to the specification is respectfully requested.

Rejection of Claims 106, 107, 109, 111 and 112 Under 35 U.S.C. §112, First Paragraph

Claims 106, 107, 109, 111 and 112 have been rejected under 35 U.S.C. §112 as well, on the grounds that the disclosure is enabling only for claims limited to the treatment of Crohn's disease with the cA2 antibody. The Examiner contends that the specification provides no guidance as to the design of anti-TNF peptides (1) which are able to bind with high affinity to TNF at residues 87-108 or residues 59-80 and 87-108; (2) which competitively inhibit binding of Mab A2; and (3) which can neutralize biological activity of TNFα with an ID50 as specified in Claims 49-51.

The Applicants respectfully submit that the Examiner is referring to an application other than the one provided by the Applicants. The application as amended contains Claims 106-112, and, therefore, does not contain Claims 49-51 or 35. The Examiner may be referring to co-pending application Serial No. 08/192,093, which formerly contained Claims 35 and 49-51, before they were cancelled on December 22, 1995. Consideration of these cancelled '093 claims should not be part of the Examiner's review of Applicants' present application. Furthermore, the rejected original Claim 112 is of the scope requested by the Examiner.

Even with the above notwithstanding, the full scope of all the present claims has been enabled by the present application. Applicants have provided sufficient guidance for the production of chimeric anti-TNF antibodies useful in the claimed invention.

The starting materials (e.g., mice, TNF antigen and myeloma cells) are available to the public. Furthermore, the methods used to prepare hybridomas and to screen them against TNF antigen were both well known in the monoclonal antibody art and adequately disclosed in the application. "Enablement is not precluded by the necessity for some experimentation such as routine screening." Wands, 8 U.S.P.Q.2d at 1404. The Wands court used the Forman factors to determine that undue experimentation was not required to produce the antibodies in that case. Ex parte Forman, 230 U.S.P.Q. 546, 547 (Bd. Pat. Appls. and Interf. 1986). In their 149-page specification, the Applicants here have surpassed the enabling description in Wands by several orders of magnitude. Throughout their specification, Applicants have described the construction and screening of the necessary chimeric anti-TNF antibodies. For construction guidance, see, for instance, Examples I-VI on pages 75-83, VIII-IX on pages 84-85, and XIII-XIV on pages 97-99. For screening guidance, see, for instance, page 76, line 23 to page 78, line 34; page 80, lines 6-13; and Examples X-XIV on pages 85-99.

Regarding enabling anti-TNF peptides which bind with high affinity to TNF at residues 87-108 or both residues 59-80 and 87-108, the Examiner stated that "the specification describes an analysis of the epitope binding specificity of exemplary monoclonal antibody A2. However, there is no description of the structural elements required of a peptide which have the above characteristics which would provide guidance to one of skill in the art in the production of immunoreceptor molecules as broadly defined by claim 35." As stated above, the application as amended does not contain Claim 35. While it is believed that the assertion is irrelevant to the examined claims, Applicants disagree. Their specification has provided ample guidance for the production of such elements. See, for example, Examples I-VI on pages 75-83, VIII-IX on pages 84-85, and XIII-XIV on pages 97-99. With regard to the competitive inhibition of Mab A2 binding, Applicants disclosed producing the antibodies with the methods

set forth in Examples I-IX, and screening them using the neutralization and inhibition assays discussed in Examples II and X. (see page 77, line 7 to page 79, line 1; page 87, lines 10-35). Finally, regarding neutralizing the biological activity of TNF-alpha with an ID50, Example XI specifically discloses such screening of chimeric anti-TNF antibodies produced by the methods disclosed throughout Examples I through X of the specification. (See also Examples XV and XVI).

Therefore, Applicants have taught the production of chimeric antibodies having specificity for the TNF antigen and have claimed this as their invention. They have provided several examples of such antibodies which retain specificity for the antigen defined by the murine A2 antibody. They have also disclosed sequences of the cA2 variable regions, disclosure of which allows one skilled in the art to construct additional chimeric molecules specific for the TNF antigen, without needing to clone the anti-TNF antibody variable regions de novo, as Applicants have done.

The Examiner has also objected to the application as lacking enablement of the invention with respect to small bowel Crohn's disease. He indicated that the Murch reference teaches that TNFα is elevated only in individuals with large bowel Crohn's disease and that the etiologies of small and large bowel Crohn's disease are different with respect to serum TNF levels and, therefore, treatments of one type of disease would not work for the other. The Examiner stated that undue experimentation would have been required to practice the small bowel embodiment of Crohn's disease at the time the application was filed. However, the Examiner himself cited Sun et al. (J. Clin. Invest., 81:1328-1331, 1988) in the Office Action section entitled "Claim Rejections - 35 U.S.C. §103." Sun et al. explicitly teach that TNF induces necrosis of the small bowel. (see, for example, page 1329, col. 1, first full par.) Therefore, the teaching in Sun et al. refutes the notion that treatment with a TNF inhibitor would necessarily only have an effect on Crohn's disease of the large

bowel. Furthermore, Claims 106-112 specifically claim methods of treating TNFα-mediated disease. As such, even if the disease state exemplified by the Examiner is not mediated by TNF-α, then the claims do not embrace its treatment. Withdrawal of the rejection is requested.

The Examiner has also indicated that the claims should be limited to cA2. He stated that A2 is a murine monoclonal antibody and that it is well established that the human body will mount a strong HAMA (human anti-murine antibody) response to murine antibodies which are administered in vivo, and therefore, undue experimentation would be required to practice the instant invention with any antibody other than cA2.

The Applicants state in the specification on page 36, lines 12-14, "murine MAbs are undesirable for human therapeutic use, due to a short free circulating serum half-life and the stimulation of a human anti-murine antibody (HAMA) response." For this reason, all of the claims in the Applicants' application are directed to methods of treating TNFα-mediated disease in a human comprising administering to the human an effective TNF-inhibiting amount of an anti-TNF chimeric antibody. None of the claims are drawn to use of purely murine antibodies. The human constant region in the claimed antibodies has been demonstrated to increase the circulating serum half-life and decrease the immunogenicity of the antibody. Therefore, Applicants respectfully submit that the HAMA response to murine antibodies should not cause a rejection of Applicants' claims which are drawn solely to the use of chimeric antibodies.

The Examiner also directs Applicants' attention to the Rademacher reference which the Examiner states shows that the glycosylation of the antibody is extremely important in treating individuals with any allergic disorder, and Crohn's disease in particular. The Examiner, citing Ex parte Hitzeman, 9 U.S.P.Q.2d 1821, 1822 (Bd. Pat. Appls. and Interf. 1988), stated that with cases involving "unpredictable factors, such as most chemical reactions and physiological activity," a higher degree of

description is required to provide enablement. However, "it is well settled that patent Applicants are not required to disclose every species encompassed by their claims, even in an unpredictable art." In re Vaeck, 20 U.S.P.Q.2d 1438, 1445 (Fed. Cir. 1991). Furthermore, Applicants believe, in light of the discussion above regarding deposits, that the glycosylation of the antibodies produced by an animal with Crohn's disease is immaterial to the need for glycosylation of the administered antibodies in the claims. As discussed above, the Applicants have disclosed methods of production of appropriately glycosylated chimeric anti-TNF antibodies without undue experimentation. Therefore, the invention can be practiced with anti-TNF chimeric antibodies other than cA2 without undue experimentation. Withdrawal of the rejection is respectfully requested.

The Examiner has rejected Claim 109 as containing new matter and has objected to the specification for not providing support for the invention as is now claimed. Claim 109 defines the method wherein the chimeric antibody binds TNF but does not bind to amino acids 11-13, 37-42, 49-57 or 155-157 of SEQ ID NO: 1 of hTNF. The limitations appear in the specification as filed. These chimeric antibodies are defined, for example, at page 23, lines 13-17, of the specification. Thus, Applicants have provided the showing required by the Board of Appeals in Ex parte Grasselli, 231 U.S.P.Q. 393 (Bd. Pat. Appls. and Interf. 1986) and by the Examiner at page 8 of the Office Action. No new matter is added by this new claim.

The Examiner further states that "Applicants are required to claim their antibody by what it does do rather than what is does not do." It is unclear whether the Examiner is asserting that any negative limitation is improper under 35 U.S.C. 112, first paragraph. If this is the case, support for the rejection is respectfully requested. In this circumstance, Applicants have defined the antibody in terms of "what it does do." The antibody is chimeric, binds TNF and is inhibitory. Claim 109 further

defines that the epitope is not included in certain regions of the protein. In other words, the antibody of Claim 109 binds an epitope included in the remaining amino acids of the protein.

Withdrawal of the objection to the specification and the rejection of Claim 109 is requested.

Rejection of Claims 106-112 Under 35 U.S.C. §103

Claims 106-112 have been rejected under 35 U.S.C. §103 as being unpatentable over the combination of Lichtenstein (Current Opinion in Gastroenterology, 8:655-662, 1992) in view of Sun et al. (J. Clin. Invest., 81:1328-1331, 1988) in further view of Le et al. (Abstract, No. CA118(5):37480n), WO91/02078, or Möller et al. (Cytokine, 2(3): 162-169, 1990).

Teachings of the References Cited

1. Lichtenstein

The Examiner indicated that Lichtenstein teaches the involvement of TNFα in the etiology of Crohn's disease. He stated that "the reference teaches one of ordinary skill in the art that Crohn's disease is associated with elevated levels of TNF alpha and indicates that TNF alpha is present in highest concentrations at the site of necrosis."

Applicants wish to draw the Examiner's attention to the fact that this reference is dated 1992 (the precise date was not provided), a year after the March 18, 1991 filing date of the '827 application, which is a parent to Applicants' application. (See above priority discussion). Therefore, Lichtenstein is not a prior art reference for a §103 rejection of Applicants' application. Furthermore, the Lichtenstein abstract does not teach the involvement of TNFα in the etiology of Crohn's disease. It merely teaches the assessment of Crohn's disease activity with evaluation of TNFα in an animal with the disease. In fact, the abstract states that "the etiologic agents responsible for Crohn's disease and ulcerative colitis remain elusive." Moreover, in their conclusions, the authors state that "we still

have a significant path to travel until we fully comprehend these diseases and uncover their causes and cures." (Page 660, column 2, second full paragraph). Thus, Lichtenstein does not teach the inhibition of TNF activity as an effective treatment for Crohn's disease. Rather, it merely suggests examination of the presence of TNF as a diagnostic tool. One skilled in the art would not extrapolate correlation to causation and reasonably conclude that by inhibiting a factor correlated with a disease one can treat the disease. Thus, Lichtenstein does not suggest treatment of Crohn's disease, or any other TNF-mediated disease, with an anti-TNF antibody.

2. Sun, et al.

The Examiner indicated that:

> TNF is taught to be "a major cytokine that may initiate a cascade of inflammatory and coagulative events in ... tissue injury ... and ... may play an important role in the development of irreversible shock and bowel necrosis". (c.f. page 1330, last paragraph). Moreover, the paragraph bridging pages 1329 and 1330 teaches one of ordinary skill in the art that TNF mediates PAF release. Therefore, the Sun reference would have taught one of ordinary skill in the art that anything that inhibits TNF would also inhibit PAF, because PAF is released by serum TNF. Moreover, the reference teaches at the last sentence of the abstract that "TNF-induced bowel necrosis is due to PAF release and can be prevented by pretreatment with PAF antagonists". See also the last paragraph of page 1329. Therefore, the reference clearly suggests to one of ordinary skill in the art that inhibition of TNF inhibits bowel necrosis. Accordingly, the reference provides a reasonable expectation that molecules which inhibit TNF action in vivo, would also inhibit disease associated with bowel necrosis. Crohn's disease is just such a disease.

Respectfully, this misrepresents the teachings of Sun et al. Sun et al. teach that three substances are implicated in rat bowel necrosis: TNFα, lipopolysaccharide (LPS) and platelet-activating factor (PAF). Specifically, they teach that "(a) TNF caused PAF production in bowel tissue; (b) the effects of TNF and

LPS on PAF production in the intestine are additive; (c) TNF and LPS are synergistic in inducing bowel necrosis; and (d) TNF-induced bowel necrosis is due to PAF release and can be prevented by pretreatment with PAF antagonists." The complete last sentence on page 1330, last paragraph, actually states that "[s]ince LPS administration causes production of TNF and PAF, the synergistic effects between LPS and PAF, and between TNF and LPS, may play an important role in the development of irreversible shock and bowel necrosis." (Emphasis added, cites omitted). Likewise, the paragraph bridging pages 1329 and 1330 states that "TNF and LPS also acted additively to induce local formation of PAF."

In fact, the authors noted that their previous investigations demonstrated that a dose of PAF or a high dose of LPS alone could cause ischemic bowel necrosis. (Page 1329, Col. 2, 2nd full par.). Therefore, the authors teach away from the notion that inhibition of a single substance, TNF, would prevent Crohn's disease.

Sun et al. also teach that "there seems to be a great variation in the levels of endogenous TNF production and responses to exogenous TNF administration among different species. In humans, the level of endogenous TNF production is very low." (page 1330, col. 2, 2nd full par.) In clinical trials the doses used in humans were "much lower than those used in our experiments". Thus, Sun et al. implicitly caution against use of the data from that experiment for the treatment of Crohn's disease in humans.

3. Le, et al.

The Examiner has indicated that the Le reference (WO92/16553 or its chemical abstract) teaches the preferred antibodies of the claimed invention and their use in pathological conditions associated with TNFα and removal of TNFα from body fluids. However, this reference corresponds to the published PCT application of the invention disclosed in application Serial No.

07/853,606, of which Applicants' application is a continuation-in-part. Applicants' are entitled to the effective filing date of this application, for the reasons set forth above. As such, it is not prior art against the claims.

4. Möller et al. and WO91/02078

The Examiner indicated that Möller et al. and WO91/02078 teach monoclonal antibodies which are functionally similar to the A2 antibody as characterized in the specification. The Examiner stated that in view of the similarities between the A2 antibody and Möller's M195 antibody, they appear to have the same or similar epitope binding specificities and M195 is expected to have the properties recited in the instant claims.

Although the Examiner referred to "Möller references", only one Möller reference is of record in this application. The Applicants have listed on their IDS the Möller reference entitled "Monoclonal antibodies to human tumor necrosis factor α: in vitro and in vivo application", Cytokine 1990, pp. 162-169. Since the Examiner has not listed any Möller references on the PTO-892 form, it is unclear to Applicants to which other Möller reference the Examiner is referring. The Examiner may be referring to the Möller et al. patent, U.S. Patent No. 5,231,024, which was included on the PTO-892 form in the Office Action for a sister application, Serial No. 08/192,093. Therefore, this response will address Möller references.

The claims of the present application are drawn to the use of chimeric antibodies which bind a neutralizing epitope of TNFα and, in preferred embodiments, competitively inhibit binding of the A2 or cA2 antibody to treat TNFα-mediated disease, such as rheumatoid arthritis and Crohn's disease. As disclosed in the patent application, the A2 antibody binds to an epitope of TNF which is distinct from the receptor binding site of the molecule. Thus, the claimed monoclonal antibodies in these preferred claims, in their ability to inhibit A2 or cA2 binding, must also bind to the same or similar TNF epitope.

Both Möller et al. references teach a species specific murine monoclonal antibody, mAb 195, which neutralized human TNFα in a murine animal cachexia model where a lethal dose of hTNFα was administered to Balb/c mice. The references do not teach or suggest the treatment of humans suffering from TNFα-mediated disease with a chimeric antibody. In fact, in view of the significant failures to treat cachexia or sepsis with murine antibodies, one of ordinary skill in the art would not be motivated to extrapolate these minimal results to reasonably conclude that such an antibody would be successful in treating a different TNFα-mediated disease state. Sun et al. discussed above, support this conclusion. Furthermore, there is no motivation within the references to manufacture a chimeric antibody for any purpose.

It is true that murine monoclonal antibodies which bind TNF are known. It is also true that the person of skill in the art was aware that TNF possessed multiple epitopes. However, the prior art does not describe the treatment of TNFα-mediated disease with chimeric antibodies which possess the ability to neutralize TNF or which inhibit binding of A2 or cA2 to TNF.

Furthermore, Claims 106-112 are separately patentable over these references. Known murine antibodies are exemplified in the published PCT, WO 91/02078. In this PCT, Rathjen *et al.* describe antibodies which inhibit TNF binding to its receptors. The TNF epitopes which are recognized by the antibodies are described on pages 4 and 5 therein, for example. The reference does not describe antibodies which bind to "one or more epitopes included in amino acids" between 87-108 of TNF. In fact, this region is specifically excluded from the many inhibitory epitopes described in the application. Likewise, the epitopes of the reference are not embraced within Claim 109. The person of skill in the art would not have been motivated or enabled by this reference to prepare a chimeric antibody or monoclonal antibody which recognizes the A2 epitope or will competitively inhibit A2 or cA2

binding to TNF with an expectation that the antibody will possess the ability to neutralize TNF.

Möller *et al.* also do not explicitly describe the epitopic specificity of the disclosed monoclonal antibodies. Thus, any rejection or assertion that the present claims describing antibodies of the preferred epitopic specificity are unpatentable over these references requires the assumption that the antibodies taught in these references inherently inhibit A2 binding to TNF or possess the epitopic specificity defined within these claims.

Inherency needs to be a definite result, not a mere possibility. There is nothing cited in the prior art which would suggest that antibodies which recognize the A2 epitope would neutralize TNFα. Far from being inherent, it is unlikely that any of the antibodies described in the foregoing studies are specific for the same TNFα neutralizing epitope(s) as Applicants' claimed monoclonal antibodies. The cited references do not describe *in vivo* neutralizing ability of any antibody described for use in the treatment of humans, nor do they teach the specific epitope to which the preferred antibodies of the claims bind. TNFα is known to contain many epitopes. A skilled artisan, on the basis of the information disclosed in these references, would not conclude that any of the prior art antibodies are identical to or contain the features of the antibodies claimed by the Applicants.

In distinction, the antibodies prepared herein have been demonstrated to be capable of neutralizing TNFα in a clinical setting with superior results.

Furthermore, the Examiner indicated that WO 91/02078 teaches high affinity TNF-specific monoclonal antibodies, which are shown to inhibit biological activities of TNFα and some of which bind to epitopes located within synthetic peptides corresponding to TNFα, which contain an epitope recognized by the A2 antibody. He stated that "At least some of the referenced antibodies would be expected to competitively inhibit binding of Mab A2 of the instant claims to TNF alpha and to have ID50 values recited in

the claims." First, Applicants note that the claims in the instant application, Claims 106-112, do not recite ID50 values. Thus, these arguments do not appear to be relevant to the present claims. Further, there is no technical reasoning to support the Examiner's assumption.

Therefore, Applicants respectively assert that the antibodies disclosed in WO91/02078 are not the same as the cA2 and A2 antibodies referred to in Applicants' claimed invention.

Improper Combination of the References

The Examiner indicated that:

> Knowing that cA2 or A2 can remove TNF from body fluids and knowing that removing TNF from serum would inhibit the in vivo effects of TNF because there would be a lower concentration of TNF in solution, one of ordinary skill in the art would be motivated to use cA2 or A2 to treat Crohn's disease with a reasonable expectation of success. As a result, the invention as claimed would have been clearly prima facie obvious to one of ordinary skill in the art at the time that application was filed absent unexpected results.

The Applicants respectfully disagree with this assessment. In order for references to be combined, there must be some teaching or suggestion in the prior art of record supporting the combination (ACS Hospital Systems Inc. v. Montefiore Hospital, 221 U.S.P.Q. 929, 933 (Fed. Cir. 1984)). However, no such teaching or suggestion appears in the above-cited references. Lichtenstein, Sun et al., Le et al., Möller et al. and Rathjen et al. are relied upon in various combinations. Lichtenstein, the stated primary reference, is not prior art. Le et al., relied upon to teach the antibodies of the claims and chimeric antibodies as a whole is also not prior art. The Lichtenstein and Sun et al. references do not disclose anti-TNF chimeric antibodies or their use in the claimed invention. In fact, Lichtenstein and Sun et al. do not support the conclusion that blocking TNFα activity can result in successful treatment of Crohn's disease or any other TNFα-mediated disease. Therefore, without the Le, Möller, and WO91/02078 references to teach the

claimed antibody, the obviousness rejection must fail. The Le reference is the only reference which contains the requisite teachings, but it is related to this application and is not prior art to support an obviousness rejection.

Therefore, even if the Sun and Lichtenstein references did teach that TNFα is causally linked to Crohn's disease or any other TNFα-mediated disease, there is no connection to the claimed antibody. No teaching or suggestion of a chimeric anti-TNF antibody appears in the Sun or Lichtenstein references. Furthermore, neither of these references provide the necessary motivation to combine with any other reference which would teach chimeric antibodies. One of ordinary skill in the art would not have been motivated to look beyond the general teachings of Lichtenstein and Sun regarding the relationship between TNFα and Crohn's disease to the use of the claimed anti-TNF antibody to treat the disease or any other TNFα-mediated disease. Möller et al. and Rathjen et al. simply do not overcome these deficiencies.

Nonobviousness of the Claims In View of the Combination of References

Obviousness is established only if the teachings of the cited art would have suggested the claimed invention to one of ordinary skill in the art with a reasonable degree of successfully achieving the claimed results. In re Vaeck, 20 U.S.P.Q.2d 1438, 1442 (CAFC 1991). Both the suggestion and the reasonable expectation of success must be found in the prior art, not in the applications' disclosure. Id. One of ordinary skill in the art would not have been able to predict, given the Examiner's cited references, whether the cA2 chimeric anti-TNF antibody would be effective in treating TNFα-mediated disease, with the exception of the Applicants' own reference, Le et al., improperly cited by the PTO.

Applicants have, for the first time, demonstrated the protective effect of immunization with the chimeric anti-TNF antibody to effectively treat TNFα-mediated disease. Thus, even

if the references were properly combined, the current invention would not have been rendered obvious, because one of ordinary skill in the art would not have had a reasonable expectation of success in achieving the disclosed results.

Thus, the available prior art against the present claims do not describe or suggest the preparation of chimeric antibodies which bind TNFα, do not provide a reasonable expectation of achieving an antibody of reduced immunogenicity and/or possessing a therapeutic benefit and do not reasonably suggest the unexpected and superior results achieved and described herein were possible. Thus, withdrawal of the rejection is respectfully requested.

CONCLUSION

It is respectfully submitted that the claims are now in condition for allowance. If the Examiner feels that a telephone conference would be helpful in expediting the prosecution of the application. The Examiner is encouraged to telephone the undersigned at (617) 861-6240.

Respectfully submitted,

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